REMARKS

In response to the Office Action of February 20, 2008, claims 19, 46, 47 and 53 are amended and claims 60-66 are added. Briefly, claim19 has been amended to exclude the intended use of the composition in that the Examiner has taken the position that this limitation does not patentably distinguish the composition. As a result of this amendment to claim 19, new claim 60 has been added and claims 46, 47 and 53 have been amended. Finally, new claims 61-66 have been added to better define the claimed invention. Support for the new amendments to claims can be found through the Specification (e.g. see page 1, lines 13-23, and page 3, line 15). **C**laims 19-30, 32 and 46-59 were rejected under 35 U.S.C. § 103(a). As detailed below, Applicant respectfully traverses this rejection.

The Examiner bears the burden of establishing a prima facie case of obviousness under 35 U.S.C. § 103. In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 USPQ2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). To establish obviousness, both the elements of the claimed invention plus the motivation to combine the elements must be present in the prior art. *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (PTO Bd. App. Intf., 1988).

Examination Guidelines for determining obviousness are set forth in Section 2141 of the MPEP, which provides in relevant part:

> As reiterated by the Supreme Court in *KSR* [*KSR International Co. v. Teleflex, Inc.* 550 U.S. ___, 82 USPQ2d 1385 (2007)], the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(A) Ascertaining the [scope and content of] the prior art; and
(B) Ascertaining the differences between the claimed invention and the prior art; and
(C) Resolving the level of ordinary skill in the pertinent art.

(MPEP § 2141, page 2100-116 (Rev. 6, Sept. 2007). Where the patent at issue claims a chemical compound or composition, the analysis of the second Graham factor, the difference between the claimed invention and the prior art, "often turns on the structural similarities and differences between the claimed compound and the prior art compounds." *Eisai Co. v. Dr. Reddy's Labs; LTD*, 2008 U.S. App. LEXIS 15399 (Fed. Cir. July 21, 2008). The law is clear that a *prima facie* case of obviousness is established if there is "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." *In re* Dillon, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (emphasis added). Once established, the burden then shifts to the applicant to rebut the *prima facie* case. "Such rebuttal or argument can consist of a comparison to test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." *In re* Dillon,16 USPQ2d at 1901 (Fed. Cir. 1990). As detailed below, Applicant maintains that the Examiner has not made a *prima facie* case of obviousness. Alternatively, assuming for the sake of argument that the Examiner has made a *prima facie* case, Applicant asserts that it is effectively rebutted by a showing that the claimed composition possesses properties that the prior art does not have.

The Examiner has maintained the rejection of claims 19-30, 32 and 46-59 under 35 U.S.C. § 103(a) as being unpatentable over Xu (U.S. Pat. No. 6,083,921) in view of Zhou (U.S. Pat. No. 6,319,523) for the reasons set forth in the Office Action dated February 9, 2007. Briefly, the Examiner reasons that Xu teaches a pharmaceutical composition comprised of baicalin for antibacterial purposes. The Examiner acknowledges that Xu does not teach the use of the flavan catechin, but reasons that Zhou teaches a pharmaceutical composition comprised of catechin contained within a pharmaceutical composition for antibacterial purposes. From this,

the Examiner concludes that one of ordinary skill in the art would have been motivated to modify Xu's pharmaceutical composition to include the active ingredient in Zhou's composition because the combined references would create the claimed topical pharmaceutical to be used for antibacterial purposes. Applicant respectfully traverses this rejection.

Xu teaches pharmaceutical compositions for use in preventing and treating viral and bacterial infections or for use in enhancing the immune response by increasing NK cell activity or augmenting the production of interferon-alpha. Xu does not teach or suggest that any of the disclosed compositions and/or compounds would be useful in the treatment of skin conditions. Nor does Xu teach or suggest that any of the compositions and/or compounds disclosed function as inhibitors of COX and/or LOX or that any of the compositions and/or compounds would be useful in the treatment of COX and LOX mediated diseases or conditions. Rather, Xu teaches that the disclosed compositions "are particularly suitable for treating or preventing an infection by bacteria and other viruses that affect the respiratory system." (col. 8, lines 36-41). Furthermore, there is no evidence to suggest that there would be any substantial overlap between indications requiring the use of the compositions taught by Xu and those requiring a COX/LOX inhibitor. The only teaching or suggestion regarding these compositions in general or *Scutellaria* specifically is as antibacterial, antiviral and immunomodulating substances.

Zhou teaches a composition for inhibiting oral bacteria comprised of a polyphenol derivative, preferably a catechin derivative and at least one compound selected from the group consisting of a mogroside derivative composition, licorice extract and combinations thereof (col. 1, lines 40-48). Zhou, like Xu does not teach or suggest that any of the disclosed compositions and/or compounds would be useful in the treatment of skin conditions. Nor does Zhou teach or suggest that any of the compositions and/or compounds disclosed function as inhibitors of COX and/or LOX or that any of the compositions and/or compounds would be useful in the treatment of COX and LOX mediated diseases or conditions. Rather, Zhou teaches that the disclosed compositions inhibit oral bacteria and are "effective in treating oral malodor and gum diseases, which helps prevent tooth decay and stomach acid reflux." (col. 1, line 64 - col. 2, line 1).

Furthermore, as in the case of the Xu reference, there is no evidence to suggest that there would any substantial overlap between indications requiring the use of the compositions taught by Zhou and those requiring a COX/LOX inhibitor.

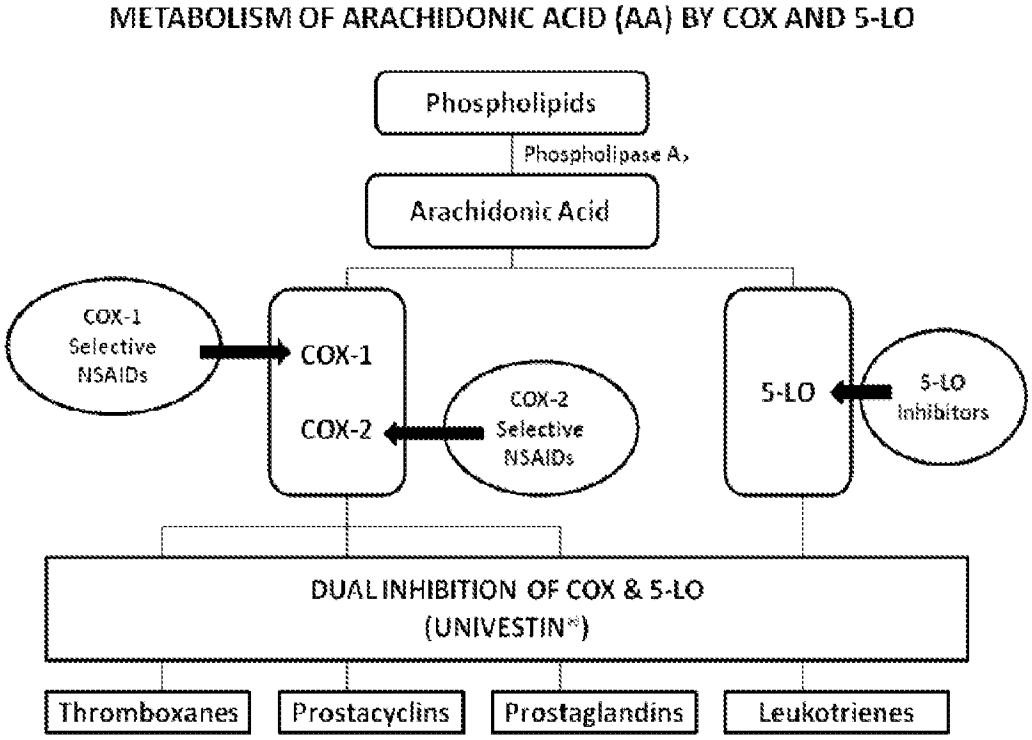
The claims of the instant invention, on the other hand, are drawn to a pharmaceutical composition of matter for use in the treatment of COX and LOX mediated diseases and conditions of the skin. The composition of matter is comprised of a mixture of Free-B-Ring flavonoids and flavans, comprising at least baicalin and catechin. There is no teaching or suggestion in either of the references relied upon by the Examiner of a composition of matter comprised of a combination of Free-B-Ring flavonoids or flavans. In fact, to date Applicant is unaware of any reports of a formulation combining exclusively Free-B-Ring flavonoids and flavans as the primary biologically active components for the treatment of any disease or condition, including those related to inflammatory conditions of the skin.

As detailed in the background section of the application, inflammation is a complex process, leading to the release of a variety of pro-inflammatory mediator molecules. Briefly, with reference to Scheme 1, when tissue is damaged the body releases phospholipids into the damaged area. The phospholipids are then converted by the enzyme phospholipase A_2 into arachidonic acid (AA), which in turn is metabolized via the cyclooxygenase and 5-lipooxygenase (COX/5-LO) pathways into thromboxanes, prostacyclins, prostaglandins and leukotrienes. These vasoactive compounds are chemotaxins, which promote infiltration of inflammatory cells into tissue. Thus, their presence serves to both initiate and prolong the inflammatory response. As a result, the enzymes responsible for generating these mediators of inflammation --COX-1/COX-2 and 5-LO-- have become targets in the development of anti-inflammatory agents.

To understand the significance of the instant invention it is important to put it into historical context. Briefly, in the 1970's it was established that aspirin and other classic non-steroidal anti-inflammatory drugs (NSAIDs) acted by inhibiting the cyclooxygenase (COX) enzyme. Approximately twenty years later, in the early 1990's, it was discovered the COX enzyme exists in two different isoforms referred to as COX-1 and COX-2, respectively.

Subsequent to this discovery it was determined that the COX-2 isoform was an inducible enzyme involved in the inflammatory response, whereas the COX-1 isoform was a constitutional enzyme which played an important role in the regulation of physiological functions including platelet aggregation, the protection of cell integrity in the stomach and maintenance of normal kidney function. Shortly thereafter it was proposed that the undesirable gastrointestinal (GI) side effects caused by these classic NSAIDs were due to COX-1 inhibition, while the beneficial anti-inflammatory and analgesic effects were related to COX-2 inhibition. This led to the development of a subclass of NSAIDS that were selective COX-2 inhibitors, such as the coxibs: rofecoxib (vioxx) and celecoxib (celebrex). Unfortunately this class of compounds was found to increase the risk of heart attack and stroke. Consequently some of these drugs, including vioxx were withdrawn from the market in 2004.

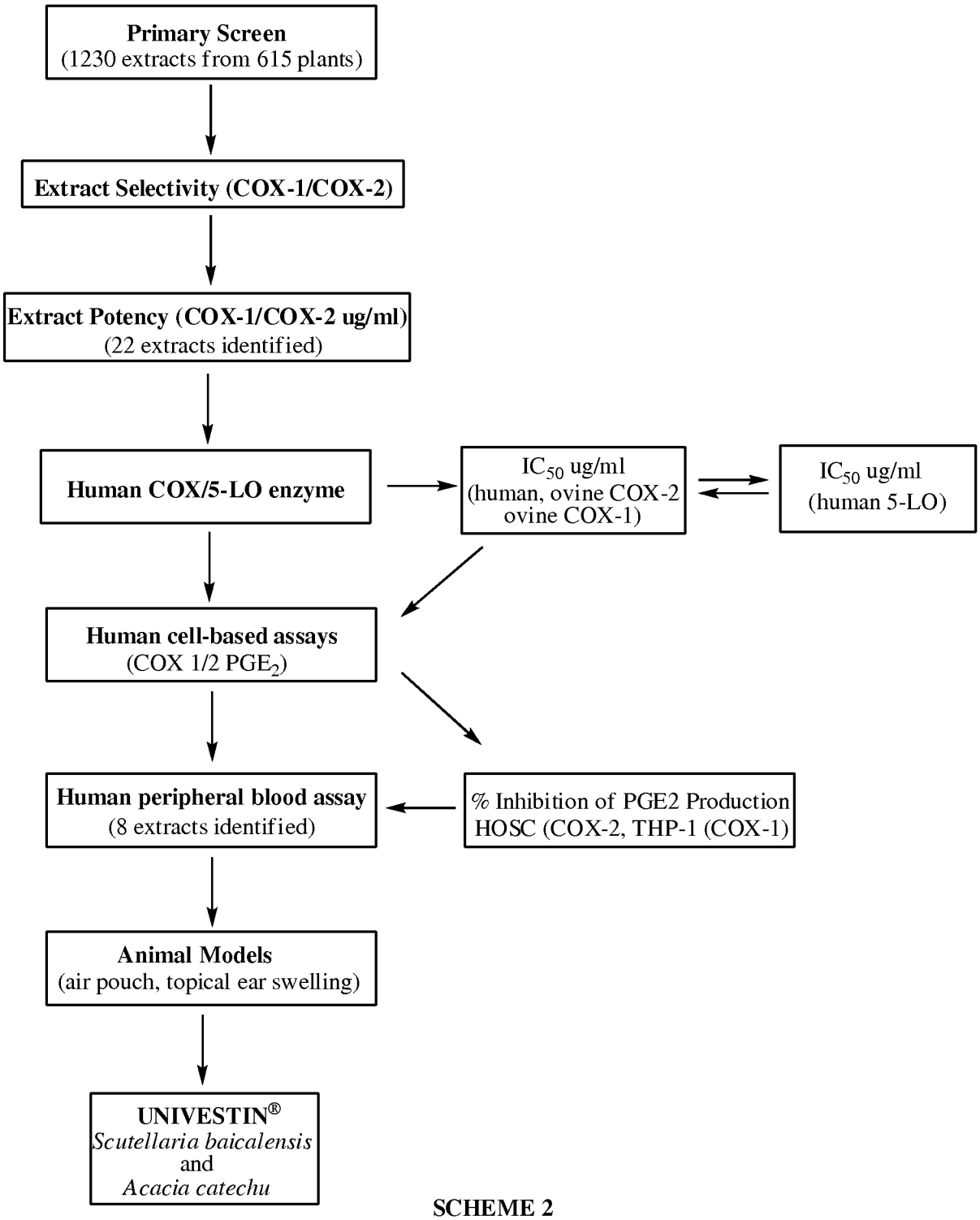
As noted above, arachidonic acid (AA) is also a substrate for the enzyme 5-lipooxygenase (5-LO), which is responsible for the production of leukotrienes (LTs). The leukotrienes generated by the 5-LO pathway have also been implicated as important mediators of chronic inflammation. LTB_4, which exhibits the most potent chemotactic activity, is elevated in the gastrointestinal mucosa of patients with inflammatory bowel disease and within the synovial fluid of patients with rheumatoid arthritis. It is worth noting that this enzyme is not regulated by either the traditional non-specific NSAIDs or by the COX-2 selective NSAIDs. It has also been postulated that inhibition of one or both of the COX enzymes may actually "shunt" the metabolism of AA down the 5-LO pathway, thereby increasing the gastrointestinal side effects associated with these compounds. In the mid to late 1990's the concept of dual COX/5-LO inhibitors as alternatives to currently available non-specific and COX-2 selective NSAIDs began to emerge. (See Kulkarni and Singh (2007) "Licofelone-A novel Analgesic and Anti-Inflammatory Agent" *Current Topics in Medicinal Chemistry* 7:251-263, a copy of which is attached as Exhibit 1).



SCHEME 1

Equipped with this general knowledge, the inventors of the referenced application invention set out to develop, from natural sources, a composition of matter that would effectively inhibit the activity of these three specific enzymes. The focus of the research was to develop a composition which would demonstrate dual specificity for COX-2 and 5-LO, while maintaining COX-2 selectivity relative to COX-1. In other words, the objective was to develop a composition that would strongly inhibit the COX-2 and 5-LO enzymes, while only moderately inhibiting the COX-1 enzyme. Their intent was to develop a composition of matter which would effectively alleviate inflammation, naturally and without the gastrointestinal side effects associated with traditional COX-1 selective NSAIDs or the adverse cardiovascular side effects associated with COX-2 selective NSAIDs.

The process utilized, referred to as Phytologix™, for the discovery and development of novel pharmaceutical, nutraceutical and cosmetic agents, focuses on documented medicinal plants and other biomaterials. It was developed by scientists at Unigen Pharmaceuticals, Inc. and an application for a U.S. patent for this process is currently pending as U.S. Application Serial No. 10/185,758, filed June 27, 2002 entitled "Method for Generating, Screening and Dereplicating Natural Product Libraries for the Discovery of Therapeutic Agents." As noted in U.S. Application Serial No. 10/427, 746 (referred to herein as the '746 application), which is incorporated into the instant Specification in its entirety (Specification, page 27, lines 3-14), using this novel process for the identification of biologically active compounds from plant sources, the inventors began by analyzing an extract library comprised of 1,230 extracts from 615 medicinal plants collected from around the world, which was created as described in U.S. Application Serial No. 10/091,362 and U.S. Application Serial No. 10/104,477, each of which is incorporated into the instant application by reference in its entirety (see Specification, page 27, lines 3-14). The basic process is illustrated in Scheme 2.


Primary Screen
(1230 extracts from 615 plants)
Extract Selectivity (COX-1/COX-2)
Extract Potency (COX-1/COX-2 ug/ml)
(22 extracts identified)
Human COX/5-LO enzyme
IC50 ug/ml
(human, ovine COX-2
ovine COX-1)
IC50 ug/ml
(human 5-LO)
Human cell-based assays
(COX 1/2 PGE2)
Human peripheral blood assay
(8 extracts identified)
% Inhibition of PGE2 Production
HOSC (COX-2, THP-1 (COX-1)
Animal Models
(air pouch, topical ear swelling)
UNIVESTIN®
Scutellaria baicalensis
and
Acacia catechu

SCHEME 2

Briefly, with reference to Scheme 2, these extracts were initially screened for their ability to inhibit the peroxidase activity associated with recombinant COX-1 and COX-2 (**Extract Potency**) and for their ability to selectively inhibit COX-2 relative to COX-1 (**Extract Selectivity**) (Specification, Example 2, pages 36-37). Using this primary screen 22 of the initial 1230 plant extracts were targeted for further study with respect to their ability to specifically and selectively inhibit COX-1 and COX-2 *in vitro* in both cell based and whole blood assays ('746 application, Example 10, pages 49-52) and for their ability to inhibit 5-LO *in vitro* (as outlined in Scheme 2). Those extracts that were efficacious in the COX-1/COX-2 and 5-LO *in vitro* assays (8 extracts identified) were then individually tested for their ability to inhibit inflammation *in vivo* using both air pouch and topical ear-swelling mouse models of inflammation when administered by multiple routes (IP and oral) ('746 application, Example 18, pages 58-59, instant Specification, Example 11, page 46). Thus, using this novel process which combines a series of *in vivo* studies as well as *in vitro* biochemical and cellular screens as described in detail in the '746 application, the inventors were able to identify from the initial 1,230 extracts isolated from 615 plants two primary extracts: *Scutellaria baicalensis* (Chinese Skullcap) extract and *Acacia catechu* (black catechu) extract. When combined, the extracts demonstrate dual specificity for COX-2 and 5-LO, while maintaining COX-2 selectivity relative to COX-1. As a result of this balance of COX-1/COX-2/5-LO inhibition, the composition effectively reduces inflammation without the gastrointestinal side effects associated with traditional NSAIDs or the adverse cardiovascular side effects associated with COX-2 selective NSAIDs. Additionally, by varying the ratio of Free-B-Ring flavonoids to flavans, Univestin® formulations having diverse antioxidant and anti-inflammatory capacity can be produced. As a result, the composition can be tailored depending upon the use and indications. Once again, this result would not have been predictable based upon the references relied upon by the Examiner.

The Examiner takes the position however, that it was *prima facie* obvious for the inventors to combine these two compositions, each of which is taught in the prior art to be useful

for the same purpose, as antimicrobials, in order to form a composition that is to be used for the very same purpose. Applicant disagrees.

As noted above, the Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex, Inc.* 550 U.S. ___, 82 USPQ2d 1385 (2007). With respect to the obviousness of a combination of elements the Court in *KSR* recognized the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does," reasoning that:

> Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR 550 U.S. at ___, 82 USPQ2d at 1396 (emphasis added). The court went on to say that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason pursue the known options within his or her technical grasp." *KSR* 550 U.S. at ___, 82 USPQ2d at 1397 (emphasis added).

As applied to the instant case, Applicant believes that the need to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the instantly claimed invention does is particularly important. As noted above, the Phytologix™ process focuses on documented medicinal plants and other biomaterials. At the time of the filing of the instant invention, Applicant was unaware of any reports of a formulation combining exclusively Free-B-Ring flavonoids isolated from plants in the *Scutellaria* genus and flavans isolated from plants in the *Acacia* genus, as the primary biologically active components for the treatment of any disease or condition, including those related to inflammation. By some

estimates there are currently between 10,000-20,000 known medicinal plants, however, some report this number to be as high as 50,000 known medicinal plants (see e.g. Wakdidar (Dec. 2004) "Global health care challenge: Indian experiences and new prescriptions" *Electronic Journal of Biotechnology* 7(3):217-223, which is attached as Exhibit 2). Although it is difficult to determine exactly how many plants have been reported as having biological activity, by a conservative estimate it is likely that at least 1000 of these plants have been reported as having some form of anti-inflammatory properties. Thus, using the following calculation:

$$(A) \times (A-1) / 2$$

when A = 1000, there are approximately 500,000 possible distinct combinations of any two of these 1000 medicinal plants known to have anti-inflammatory activity. Thus, taking into consideration only plants known to have anti-inflammatory activity there were approximately 500,000 possible combinations of any two of these plants and there is absolutely nothing in the references cited by the Examiner to suggest to one of ordinary skill in the art that the two extracts indentified by the inventors of the instant application would have been an obvious choice for combination. Especially in light of the fact that neither of these plants had been identified as dual COX/5-LO inhibitors. As discussed above, it was only after the inventors spent thousands of hours at a cost to Unigen Pharmaceuticals, Inc. in excess of 10 million dollars was the claimed combination developed via the Phytologix™ process.

Applicant would also like to refer the Examiner to the "Dictionary of Natural Products" (CRC Press (December 2007) version 16:2), a data base which lists 210,000 compounds that have been derived from natural sources. Of the 210,000 compounds, 474 are listed as having anti-inflammatory activity. Based upon these numbers alone there would have been approximately 112,000 ((474)(473)/2) combinations of any two of these anti-inflammatory compounds, with absolutely nothing to suggest to one of ordinary skill in the art that the two extracts, consisting essentially of the active ingredients baicalin and catechin, identified by the inventors of the instant application would have been the obvious choice for combination. In fact,

neither baicalin nor catechin is even listed as having anti-inflammatory activity or for that matter as having antimicrobial activity. With reference to Exhibit 3, baicalin is listed as a diuretic and catechin is listed as a having antiulcer properties. To test all of the thousands of possible combinations with no guidance whatsoever would no doubt be quite onerous to say the least, since multiple doses of each component of a given combination would have to be tested to elucidate synergistic efficacy.

The Examiner takes the position, however, that a person of ordinary skill in the art would have been motivated to employ the combination of baicalin and catechin for use in treating COX and LOX mediated diseases and conditions, because both of these compounds are known to be useful for treating microbial infections and the intended use is not limiting in that it does not create a structural difference. The Examiner reasons that "[i]t is prima facie obvious to combine two or more compositions each of which is taught in the prior art to be useful for same purpose (e.g. an antibacterial purpose), in order to form a third composition that is to be used for the same purpose." Applicant might agree with the Examiner if this were in fact this were the case and if in fact there were a finite number of plant extracts having antimicrobial activity. Additionally, in the instant case the compositions of the invention are combined to form a composition which is a dual COX/LOX inhibitor, not an antimicrobial agent, exhibiting properties that neither of the compositions alone exhibit. In a case such as this, as noted above, the law is clear that a *prima facie* case of obviousness is established only if there is a structural similarity between claimed and prior art subject matter and if the prior art gives reason or motivation to make the claimed compositions. Contrary to this however, as delineated above, there were literally thousands of possible combinations for Applicant to choose from with absolutely nothing to suggest that the two extracts, consisting essentially of the active ingredients baicalin and catechin, identified by the inventors of the instant application would have been the obvious choice for combination. Applicant asserts that the instant case is analogous to the post KSR case decided by the court in *Takeda Chemical Industries , LTD v. Alphapharm PTY., LTD*, 492 F.3d 1350, 83 USPQ 2d 1169 (Fed. Cir. 2007). In holding that the claimed composition of matter was not obvious over the

reference at issue, the court reasoned relying on the KSR decision that "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda Chemical Industries, LTD* 492 F.3d at 1359.

It is also worth noting that although plants in these two families (*Scutellaria* and *Acacia*) have been used extensively throughout the world as components of traditional herbal medicines for at least 1000 years (see Levy *et al.* (2007) "Safety and efficacy of flavocoxid compared with naproxen in subjects with osteoarthritis of the knee: a pilot study," International Cartilage Repair Society World Congress (ICRS), page 4, col. 2, which is attached as Exhibit 4), to the best of Applicant's knowledge prior to the filing of the '746 application, from which this application claims the benefit, the instant application they had not been combined as the two major active components for the treatment of <u>any</u> medical condition, including inflammation and the Examiner has presented no evidence to the contrary. Thus, lending support to Applicant's contention that there is absolutely nothing to suggest to one of ordinary skill in the art that the two extracts identified for combination by the inventors of the instant application would have been an obvious choice. On this basis, Applicant asserts that a prima facie case of obviousness has not been established.

Applicants further submit that even assuming for the sake of argument that *prima facie* obviousness had been established, it is rebutted by a showing that the claimed compositions possess unexpectedly improved properties or <u>properties that the prior art does not have</u>." *In re* Dillon,16 USPQ2d at 1901 (Fed. Cir. 1990).

As noted above, the inventors using a novel process combining *in vivo* studies as well as *in vitro* biochemical and cellular screens have developed a novel composition of matter comprised of a blend of two plant extracts --*S. baicalensis* and *A. catechu*-- which metabolically balances the inhibition of COX-1 and COX-2 and provides a comparable amount of inhibition of 5-LO in the conversion of AA to its pro-inflammatory metabolites. As a result of this balance of COX-1/COX-2/5-LO, the composition effectively reduces inflammation without the

gastrointestinal side effects associated with traditional NSAIDs or the adverse cardiovascular side effects associated with COX-2 selective NSAIDs. Thus, as noted above, this is not a case in which two or more compositions each of which is taught in the prior art to be useful for same purpose (e.g. an antimicrobial purpose), have been combined in order to form a third composition that is to be used for the same purpose. Rather the inventors have used a novel process to develop a composition of matter comprised of two specific plant extracts out of a possible 500,000 choices, having special properties, not exhibited by either extract alone, which would in no way have been predictable based upon the art cited by the Examiner. As such, Applicant submits that assuming that *prima facie* obviousness has been established it is effectively rebutted.

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: August 20, 2008

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